# The British Veterinary Journal

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NOTICE TO CONTRIBUTORS

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## *EDITORIAL*

### THE INCREASE IN THE NUMBER OF VETERINARY SURGEONS

THE report of the Council of the Royal College of Veterinary Surgeons for the year ending March 31st, 1958, contains a statistical review of the number of the members on the register over the period of years between 1935-1957. It will be noted that during that relatively short term the figure has increased by almost one hundred per cent. In 1957 there were 6,355 names as against 3,458 at the beginning of 1935. It would appear that this increase will continue, for the schools are full to repletion and there are many who have fulfilled the preliminary educational requirements, but for whom no place is available at the present time or in the immediate future. The profession basks in the splendour of full employment and a young graduate is in the enviable position of being able to pick or choose his job. The optimists, and particularly those who have only known the time of prosperity during the last twenty years, say that there is room for a still greater increase; there are others, and they are generally old enough to remember the inter-war period of depression, who are of a different opinion, and view the figures with misgiving and, in some cases, a degree of alarm. There have been occasions in the past when members of our own profession have been unable to find employment. The last time when this situation was reached was in the 1938-42 era. At that time many veterinary surgeons had to seek alternative means of livelihood or work for a pittance below that allocated to a general labourer. Veterinary surgeons were not alone in their troubles, for men of other learned professions, chemists, engineers, biologists and even medical graduates, were in a similar plight. The 1914-18 world war was the first great war in which the scientific "boffin" came into his own and the men in the laboratory were as important as those who directed affairs in the field. During the emergency, men with scientific qualifications enjoyed a time of great power and prosperity. They were at a premium. During and after the war

thousands flocked to join their ranks only to find that, when the crisis was passed, they had entered upon a career in which the potential applicants for situations far outnumbered the number of places. In recent years a similar position has confronted our sister profession of human medicine. The number of graduates has increased greatly and young doctors, and particularly those who have attained a specialist qualification, do not find suitable posts easily.

What is the cause of the great increase in the number of veterinary students and graduates? The answer would appear to be a simple one—more work. What is the manner of this work which has led to full employment and the doubling of the number of names on the register?

There are several answers to this question. Two are cogent to the present discussion. The first is the increased amount of work arising from the stimulus of war and its consequences. When the free flow of food from overseas is interrupted, home agriculture always comes into its own and the industry attains a priority and importance far beyond that accorded in time of peace. Farmers prosper, the value of their stock soars, and veterinary surgeons profit in due proportion. The second answer devolves from the Government's programme for the eradication of tuberculosis from our cattle. The great scheme, now nearing completion, has brought much work to the profession and particularly to those who practise in rural areas. Practices in which one man could fain derive a reasonable competence have been able to provide employment for several men and the remuneration has been good. Now that the programme is within two or three years of a successful conclusion and in the near future all the cattle of this country will be attested as being free from tuberculosis, it is reasonable to suppose that the surge of work will abate. Will the practices be able to carry the same manpower that they have done in the immediate past, bearing in mind that the number of the clients has not shown an increase in proportion to the work done? Of course, there are other diseases, such as Johne's Disease, waiting to be tackled. Johne's Disease probably has a more serious effect upon the efficiency of our cattle than tuberculosis. If a comprehensive programme for its eradication could be implemented, then the profession could look forward to at least another twenty years of prosperity and there would be employment for many more veterinary surgeons.

Can such a programme be implemented at the present time? There is a reasonably efficient test for tuberculosis. Is there one for Johne's Disease? If such a test can be evolved, our students and graduates can face the future with confidence. If it is not forthcoming the present pleasant zephyrs may blow cold.

# STUDIES WITH AVIANISED STRAINS OF THE ORGANISM OF CONTAGIOUS BOVINE PLEUROPNEUMONIA

## V. EXPERIMENTS WITH AVIANISED VACCINES AT VARIOUS LEVELS OF ATTENUATION

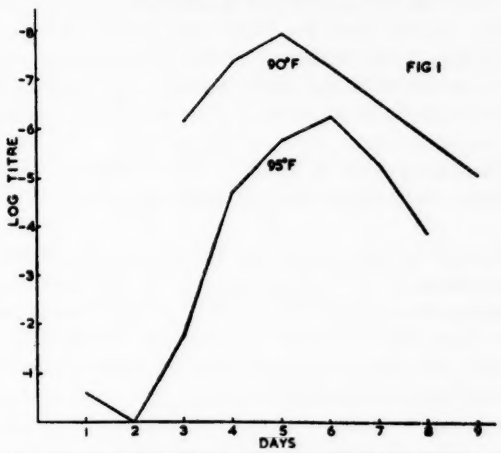
By S. E. PIERCY * and G. J. KNIGHT

*East African Veterinary Research Organization, Muguga, Kenya*

The previous article (Piercy and Knight, 1957) emphasised that although good results have generally followed the use of strain $T_1$ attenuated avianised pleuropneumonia vaccine, of which over two million doses have now been used in East Africa, the possible advantages of a stronger type of vaccine prepared from lower egg-passage levels has not been forgotten. Despite the danger of undesirable reactions, the creation of a solid and durable immunity against bovine pleuropneumonia is more likely to be achieved with comparatively virulent vaccines than with highly attenuated ones. Those with experience of the old broth culture type of pleuropneumonia vaccine recognise that attentuation to the point of complete safety results in a product of poor immunising ability and there is now a sufficient accumulation of field evidence in East Africa to indicate that highly attenuated avianised pleuropneumonia vaccines may also fail to stimulate an immunity sufficient to withstand exposure to virulent outbreaks. We have therefore carried out a number of laboratory trials with routine and experimental batches of vaccine prepared from organisms at widely differing levels of egg passage. In addition, the effect of varying the dosage and ratio of egg to organism in the inoculum has been studied.

### Materials and Methods

The strains of *A. mycoides* used and the techniques employed differed in no

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significant way from those described (Piercy and Knight, 1956, 1957). Two further investigations are briefly described below.

(i) *Growth curve at* 90° F. Following the finding that an incubation temperature of 90° F. results in significantly higher yields of organisms in inoculated eggs than 95° F., the growth curves of strain $T_1$ in eggs incubated at the two temperatures were compared (Fig. 1).

Although the pattern of the two curves is essentially the same, the peak titres reached at 90° F. were higher than at 95° F. Furthermore the logarithmic phase of multiplication began a day earlier at the lower temperature. The 90° F. growth curve confirmed the improved yield of organisms and showed that third day deaths may usefully be included in the harvest during vaccine production, thus increasing the number of doses to be obtained from a given number of eggs.

(ii) *The significance of amount of inoculum on yield of organisms.* Groups of 20 eggs were inoculated with strain $T_3$, generation 8, using freshly harvested embryos diluted $10^{-3}$, $10^{-6}$ and $10^{-8}$ respectively. Eggs dying on the sixth day after inoculation were harvested from each group and titrated separately. Table 1 reveals that the yield of organisms was not significantly affected by varying the dose of inoculum.

TABLE 1
*The effect of dosage on yield of organisms*

| Inoculum | Day of Harvest | Titres |
|---|---|---|
| T3/8, $10^{-3}$ | 6 | 6.00 |
| ,, $10^{-6}$ | 6 | 6.35 |
| ,, $10^{-8}$ | 6 | 6.20 |

## Results

I. *Trials with routine batches of vaccine at widely differing levels of egg passage.*

Six batches of vaccine were used. Three of them (M/8, M/9 and M/10) were prepared at Muguga from generation 44 of the stock vaccine strain $T_1$ (Sheriff and Piercy, 1952) and three* (K.137, K.162 and K.185) were prepared at the Veterinary Research Laboratory, Kabete, from the 137th, 162nd, and 185th generations respectively of the same strain. Each batch was inoculated subcutaneously into groups of ten cattle at normal field dilutions and after a period of six weeks' observation, during which no clinical reactions of any sort were observed, all the groups, together with 10 uninoculated control animals, were challenged with 1 ml. of a culture of *A. mycoides* in the filamentous stage of growth. One of the control animals died of another disease before a challenge reaction could develop. Table 2 records the results.

With only 10 cattle in each group, the results are not sufficiently decisive to permit a ready assessment of the relative values of the different vaccines, especially as a greater proportion than usual of fully resistant animals was encountered amongst the control group. Since our experience has been that usually only a small number of fully resistant cattle are encountered and since the challenge culture was virulent, it is reasonable to assume that the high percentage (44 per cent) of resistant animals amongst the controls was a matter of chance. It seemed, therefore, that an appro-

* Kindly supplied by the Chief Veterinary Research Officer, Kabete.

TABLE 2

*The immunising value of attenuated avianised pleuropneumonia vaccines at various egg-passage levels (strain $T_1$).*

| Batch | Egg passage level | Estimated log no. of organisms per dose. | Vaccine reactions | CHALLENGE | | | Fully immune. |
|---|---|---|---|---|---|---|---|
| | | | | Reacted & died. | Reacted & survived. | No reaction | |
| M/8 | 44 | 5.73 | 0 | 3 | 1 | 6 | 60% |
| M/9 | 44 | 5.95 | 0 | 4 | 0 | 4(A) | 50% |
| M/10 | 44 | 5.90 | 0 | 2 | 3 | 5 | 50% |
| K137 | 137 | 3.65 | 0 | 1 | 4 | 5 | 50% |
| K162 | 162 | 4.65 | 0 | 2 | 4 | 4 | 40% |
| K185 | 185 | 3.65 | 0 | 2 | 0 | 8 | 80% |
| Controls | - | - | - | 4 | 1 | 4(B) | 44% |

A. Two animals died before challenge from other causes.
B. One animal died soon after challenge from another cause.

priate way of analysing the data was to compare the challenge results in the vaccinated groups with data accumulated from previous and present challenges of control animals. The following procedure was adopted.

At the time the present trials were completed, a total of 47 control animals had been challenged in connection with various vaccine tests, using the same standard method of challenge throughout (Piercy and Knight, 1957). The results of these challenges are given below in Table 3.

TABLE 3

*Challenge results in uninoculated control animals*

| Reacted and died | Reacted and recovered | No reaction | Total |
|---|---|---|---|
| 26 (55.33%) | 14 (29.78%) | 7 (14.89%) | 47 |

The percentages of the three classes of reaction are taken as estimates of the response of a population of unvaccinated cattle to a standard challenge and are also the estimated response among vaccinated cattle on the null hypothesis that vaccine is without effect.

The three Muguga batches of vaccine were prepared in as nearly a similar manner as possible from the same seed bank and were considered to be of average quality. The accumulated result of the trials with these three batches, classified in the same three reaction categories just described, is given in the first row of Table 4.

TABLE 4

*Challenge results in cattle inoculated with strain $T_1$/44 vaccine*

| | Reacted and died | Reacted and recovered | No reaction | Total |
|---|---|---|---|---|
| Observed .. .. .. | 9 | 4 | 15 | 28 |
| Expected (Null hypothesis) | 15.49 | 8.34 | 4.17 | 28 |

The second row of this table gives the results expected on the null hypothesis that the vaccines were without effect, that is the 28 vaccinated cattle are divided in the same proportions as observed among the 47 control animals.

The figures in Table 4 strongly suggest that the observed proportions are not the same as the proportions expected on a null hypothesis. The table is in a form suitable for the application of the $X^2$ test except for the fact that the expected frequency of the class " No reaction " is less than the usually accepted minimum of five. However, by pooling the classes " Reacted and recovered " and " No reaction," a $2 \times 1$ table is obtained to which Yates correction for discontinuity may be applied, giving a value for $X^2$ of 5.18. This result is significant at the 5 per cent level, the value for " p " being $0.05 > p > 0.02$, and disproves the null hypothesis. It may therefore be accepted that the Muguga vaccines were efficacious to a degree.

Application of the same principle of analysis to the three Kabete vaccines results in the figures recorded in Table 5.

TABLE 5

*Challenge results in cattle inoculated with strain $T_1$ vaccine at egg-passage levels 137, 162 and 185.*

| | Reacted and died | Reacted and recovered | No reaction | Total |
|---|---|---|---|---|
| Observed .. .. .. | 5 | 8 | 17 | 30 |
| Expected .. .. .. | 16.60 | 8.93 | 4.47 | 30 |

Calculating the value of $X^2$ the same way as for Table 4, a value of 19.732 is obtained, the value for " p " being less than 0.001, a highly significant result which disproves the null hypothesis. The higher value obtained for $X^2$ with the Kabete vaccines is almost entirely accounted for by the more favourable survival rate amongst animals which reacted to challenge. The proportion of animals which showed no reaction to challenge and were therefore solidly immune was almost identical with both groups of vaccines.

The conclusion to be drawn from these experiments is that both the Kabete and Muguga vaccines, at widely differing egg-passage levels, conferred a significant degree of protection against a standard challenge of virulent culture. So far as solid immunity is concerned, the protection was of a similar order with both vaccines.

II. *The effect of variations in dosage, route of inoculation and egg/organism ratios on the immunity conferred by attenuated strain $T_1$ vaccines.*

Since the experiments described in the previous section indicate that strain $T_1$, whether used at the 44th or the 185th generation, is only capable of stimulating an absolute immunity against " needle " challenge in a proportion of animals, a number of variations in the composition of the inoculum and in methods of administration were studied. These were variations in the total number of organisms inoculated, in the ratio of egg constituents to organisms in the inoculum, in the route of inoculation used and in the number of inoculations given. It was appreciated at the outset that the limited number of animals and pasture accommodation available would prevent an adequate statistical examination of the results. Nevertheless, it

seemed possible that one or more indications of promising lines for future research on a larger scale might emerge from these trials.

Advantage was taken of the necessity to test two routine batches (M/11 and M/12) of Muguga vaccine, representing the 163rd and 186th generations respectively of strain $T_1$. These batches were prepared in exactly the same way, their titres (7.9 and 8.0) were almost identical, and they can be considered strictly comparable. That the difference in generations of seed material used need not be considered a significant factor is evident from the information obtained from the experiments described in the previous trial. Six groups of ten cattle were inoculated as follows:

*Group I.* M/11 vaccine. Routine field dose of 1.0 ml. of a 1/100 dilution subcutaneously. *Group II.* M/11 vaccine. Three 1.0 ml. subcutaneous inoculations at weekly intervals, using increasingly stronger dilutions of 1/100, 1/50 and 1/10. *Group III.* M/12 vaccine. 2.0 ml. subcutaneously of a 1/100 dilution containing 1 per cent dried egg. *Group IV.* M/12 vaccine. 1.0 ml. subcutaneously of a 1/50 dilution containing 2 per cent dried egg. *Group V.* M/12 vaccine. 0.2 ml. into the tail tip of a 1/10 dilution containing 10 per cent dried egg. *Group VI.* Control animals.

All groups were negative to the rapid slide agglutination test at the time of vaccination. No clinical reactions, other than a few transient temperature elevations, were observed over a period of 6 weeks when all but 5 animals in Group I were challenged. These 5 animals were to be challenged at a later date to obtain information on immunity regression, but this was not done owing to an outbreak of disease on the estate. Table 6 records the results.

TABLE 6

*Strain $T_1$ vaccines. The effect of variations in dose, route of inoculation and ratio of egg material to organisms.*

| Group | Vaccine batch | Dose | Dilution | Ratio of egg to Organisms | Estimated log. no. of organisms per dose. | CHALLENGE | | | Fully Immune. |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Reacted & died. | Reacted & recovered | No reaction | |
| I | M/11/163 | 1.0 ml. s/c | $10^{-2}$ | 1% | 5.9 | 1 | 3 | 1 | 10% |
| II | M/11/163 | 1.0 ml. s/c | $10^{-2}$ | 1% | 5.9 | | | | |
| | | " | $10^{-1.7}$ | 2% | 6.21 | | | | |
| | | " | $10^{-1}$ | 10% | 6.9 | 0 | 3 | 7 | 70% |
| III | M/12/186 | 2.0 ml. s/c | $10^{-2}$ | 1% | 6.31 | 2 | 4 | 4 | 40% |
| IV | M/12/186 | 1.0 ml. s/c | $10^{-1.7}$ | 2% | 6.31 | 3 | 3 | 4 | 40% |
| V | M/12/186 | 0.2 ml. t/t | $10^{-1}$ | 10% | 6.31 | 1 | 2 | 6 | 66% |
| VI | Controls | - | - | - | - | 3 | 7 | 0 | 0 |

Because of the small number of animals used, a statistically sound comparison between groups is not possible. If it be assumed, for the moment, that no one method of vaccination was more effective than another and the variations in result were due to chance, Groups I to V can be combined and the results studied from the simple standpoint of the degree of protection provided by strain $T_1$ vaccines. Since in our experience a fairly high proportion of uninoculated control animals are partially resistant to the subcutaneous challenge of highly virulent cultures, that is they react but recover, a comparison of vaccinated animals against any one small group of controls, which may happen to contain by chance an unduly high proportion of comparatively resistant animals, may not always result in a true interpretation. We

consider, therefore, that for the time being, until a sufficient number of controls have been challenged, the best way to obtain accurate comparisons is to compare the results in vaccinated groups with progressive accumulations of the reactions of control animals to challenge. The results with Groups I to V in Table 6, therefore, are compared with the accumulated total of 57 challenged controls and assessed, as in the preceding trial, on the null hypothesis that the vaccines were without effect.

In Table 7, the first row shows the numbers of control cattle which fall into the categories " Reacted and died," " Reacted and recovered " and " No reaction." The second row shows the observed results of the five groups combined together, and the third row gives the results expected on the null hypothesis that the vaccines were without effect, that is the 44 cattle are divided in the same proportions as observed among the 57 control animals.

TABLE 7

*Challenge results in cattle inoculated with strain $T_1$ vaccines.*

| Cattle | Reacted & died. | Reacted & recovered | No reaction | Total |
|---|---|---|---|---|
| Controls (observed) | 29 | 21 | 7 | 57 |
| Vaccinated (observed) | 7 | 15 | 22 | 44 |
| Vaccinated (expected) | 22.89 | 16.21 | 5.40 | 44 |

Application of the $X^2$ test results in a figure of 60.76 with two degrees of freedom and the value for " p " is less than 0.001. This is a highly significant result and disproves the null hypothesis. Further confirmation is thus obtained that strain $T_1$ vaccines confer a significant degree of protection against " needle " challenge.

III. *Trials with avianised vaccines of higher virulence.*

A number of experiments were made with strain $T_3$, normally used as challenge material in serum-broth culture, after adaptation to embryonated eggs. No difficulty was experienced in growing this strain in embryonated eggs and it was tested in cattle at the 11th, 28th and 33rd egg generations. In each case experimental batches of vaccine were prepared according to the standard procedure (Piercy and Knight; 1957), titrations of dried material made and the number of organisms per dose estimated. Since it was expected that the organisms at the various levels tested would still be relatively virulent, the tail-tip route of inoculation was used in some of the trials to minimise the possibility of vaccine reactions. Table 8 records the results.

No statistical examination is necessary to reveal the significant improvement in the immunity engendered by vaccines containing comparatively virulent organisms. Whereas, with eleventh passage material, 34,000 organisms per dose were sufficient to cause a 100 per cent immunity, over two million organisms per dose were necessary to achieve the same result with thirty-third passage material. It seems likely that had a greater number of organisms per dose been used at the 28th generation a more favourable result would have been obtained. It is also evident that despite

TABLE 8

*The immunising value of strain $T_3$ at various levels of egg-passage.*

| Egg generation | Route | Dose | Dilution | Estimated log. no. of organisms per dose. | No. of cattle inoculated | Vaccine reactions | CHALLENGE | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Reacted & died | Reacted & recovered | No reaction | Fully immune. |
| 11 | t/t | 0.1cc. | $10^{-1}$ | 5.129 | 10 | 3(2 Mild. 1 died.) | 0 | 0 | 9 | 100% |
| | t/t | 0.1cc. | $10^{-2}$ | 4.129 | 10 | 0 | 0 | 0 | 10 | 100% |
| | t/t | 0.1cc. | $10^{-3}$ | 3.129 | 10 | 0 | 2 | 5 | 3 | 30% |
| Controls | - | - | - | - | 10 | - | 6 | 4 | 0 | 0% |
| 28 | s/c | 1.0cc. | $10^{-2}$ | 4.45 | 20 | 1 (died) | 1 | 6 | 12 | 64% |
| Controls | - | - | - | - | 20 | - | 12 | 6 | 2 | 10% |
| 33 | s/c | 1.0cc. | $10^{-1}$ | 7.43 | 8 | 0 | 0 | 0 | 8 | 100% |
| | s/c | 1.0cc. | $10^{-2}$ | 6.43 | 8 | 2(local only) | 0 | 0 | 8 | 100% |
| | s/c | 1.0cc. | $10^{-3}$ | 5.43 | 8 | 0 | 1 | 3 | 4 | 50% |
| | s/c | 1.0cc. | $10^{-4}$ | 4.43 | 8 | 0 | 3 | 1 | 4 | 50% |
| Controls | - | - | - | - | 8 | - | 4 | 2 | 2 | 25% |
| 33 | t/t | 0.1cc. | $10^{-1}$ | 6.43 | 13 | 1(severe local) | 0 | 0 | 8* | 100% |
| | t/t | 0.1cc. | $10^{-2}$ | 5.43 | 8 | 0 | 1 | 2 | 5 | 62.5% |
| | t/t | 0.1cc. | $10^{-3}$ | 4.43 | 8 | 0 | 2 | 4 | 2 | 25% |
| Controls | - | - | - | - | 10 | - | 4 | 1 | 4 | 44.4% |

* Five animals not challenged.

this indication of attenuation, thirty-third generation material was still sufficiently virulent to cause a percentage of local reactions whether inoculated subcutaneously or into the tail-tip.

## Discussion

The trials with strain $T_1$ attenuated vaccines demonstrate that they confer a significant degree of protection against challenge. Progressive passage through embryonated eggs has not so far lessened their immunising ability for the results at generation 185 were apparently better than at generation 44.

Efforts to increase the immunising ability of strain $T_1$ vaccines by varying the dose, inoculation route and egg/organism ratio were not significantly successful, the overall mean (Table 6) of fully immunised animals remaining well below 100 per cent.

When strain $T_3$ vaccines, containing more virulent organisms, were used a highly significant improvement resulted, all animals being solidly immunised on a number of occasions. It is clear also from Table 8 that the number of organisms inoculated qualifies in some degree the number of animals immunised, and as attenuation proceeds there is a corresponding rise in the minimum dose required. Unfortunately, a percentage of severe local reactions still occurred at generation 33, whether the subcutaneous or the tail-tip route of inoculation was used. It would seem, therefore, that further attenuation of strain $T_3$ is desirable although there is a danger that immunising ability may be reduced during the process.

These experiments re-emphasise the difficulty of immunising cattle against contagious bovine pleuropneumonia under East African conditions where vaccine reactions and losses must be strictly confined. Well attenuated strain $T_1$ vaccines have proved acceptable to the African stockowner but our work has shown that a proportion of animals are not protected against a laboratory challenge. It seems probable that complete protection can only be achieved by using more virulent organisms with the attendant risk of undesirable vaccine reactions and some losses.

A reason must be sought for the inability of strain $T_1$ organisms to immunise all cattle against a laboratory challenge. A study of our challenge results shows that a considerable number of uninoculated control cattle possess a natural degree of resistance which enables them to recover from the inoculation of a virulent challenge strain after varying degrees of reaction. A small proportion are naturally fully resistant and the remainder fully susceptible. Reference to the challenge results in control animals of workers in the Sudan and Australia (Priestley 1952, 1955, Priestley and Karib 1954; White 1955; Seddon 1953) reveals a similar picture of susceptible, resistant and semi-resistant groups. Table 7 records that of 57 control animals 29 were fully susceptible, 21 were partially resistant and 7 were fully resistant. In our opinion this " middle group " of semi-resistant animals explains the failure of strain $T_1$ vaccines to immunise the whole of a population for in the majority of such animals the attenuated organisms are probably unable to propagate. The immune state of this " middle group " is largely unaffected, therefore, by vaccination although insufficiently strong to withstand experimental challenge or severe natural exposure. In this connection it is of interest to refer to Tables 4, 5 and 7 where the three types of reaction to challenge are recorded, for purposes of the " null-hypothesis " theory, under the headings " observed " and " expected." In the columns " Reacted and died " and " No reaction," there is an obvious and significant reversal of proportions as between " observed " and " expected," but the figures for the " middle groups " of animals which reacted but recovered remain substantially unchanged.

Another point of interest emerges when the percentage figure for the " middle group " of challenged control animals (Table 7) is compared with the overall percentage figure for the " middle group " of animals challenged after inoculation with $T_1$ vaccines in experiments I and II. Whereas of 57 control animals, 21 or 37 per cent reacted and recovered, 27 out of 102 or 26 per cent of animals inoculated with strain $T_1$ vaccines reacted and recovered. There is thus an indication that strain $T_1$ vaccines will overcome the resistance and thus immunise a small proportion of the " middle group." This may be the explanation of the apparently better result obtained by repeated inoculations at weekly intervals (Table 6, group II) for it seems possible that each successive inoculation immunised a further small proportion of the " middle group " of semi-resistant animals.

Unless the efficacy of strain $T_1$ attenuated vaccines can be improved, the only way to immunise these semi-resistant animals would appear to be by using more virulent vaccines. A logical approach would be to use strain $T_1$ vaccine first, thus immunising the fully susceptible proportion of a given population, and to follow this at an appropriate interval with more virulent vaccine. Since it seems fairly certain that unfavourable reactions following the use of comparatively virulent vaccines are largely confined to the fully susceptible proportion of the population, the adoption of such a method, which is analogous to the " vaccine-virus " approach in certain virus diseases, should result in the eventual protection of the whole population without the risk of undesirable vaccine reactions.

## Summary

1. A number of experiments with strain $T_1$ attenuated avianised pleuropneumonia vaccines are described. Although these vaccines conferred a significant degree of

protection against challenge with virulent cultures of *A. mycoides*, they did not create a 100 per cent immunity.

2. The existence of a proportion of naturally semi-resistant animals is considered to be the probable explanation of the failure of well-attenuated vaccines to immunise the whole of any given cattle community.

3. Total immunisation was achieved by using more virulent vaccines containing organisms at lower egg-passage levels. A small percentage of severe vaccine reactions, however, occurred.

4. It is suggested that in circumstances where vaccine reactions must be strictly confined, a logical approach might be to use strain $T_1$ attenuated vaccine in the first place, followed by a second inoculation with more virulent vaccine to immunise the semi-resistant proportion of the cattle population.

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# STUDIES ON BRACKEN POISONING IN CATTLE

## PART V

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THE chief symptoms of bracken poisoning in cattle arise from the main lesion, which is a progressive failure of the blood forming tissues. Preliminary dullness and anorexia, with mucosal discharges, are quickly followed by pyrexia, and petechial hæmorrhages or hæmorrhagic discharges. The most obvious, and also the most serious clinical signs are these hæmorrhages, followed rapidly in many cases by sloughing of mucous membranes. Once this stage is reached, prognosis is very grave, and almost always the disease is fatal. Evans, Evans and Hughes (1951, 1954), Naftalin and Cushnie (1954), attempted to reverse the course of the disease by injections of the "B group" of vitamins and others, but were completely

unsuccessful. An attempt to protect against the condition by using large doses of thiamine, vitamin $B_{12}$*, Folic acid and Leucovorin † was made by the present workers and will be described later in this paper. It was equally unsuccessful.

It is now clear that the cattle disease is not a nutritional deficiency *per se*, but is caused by a bone-marrow poison (see Part IV). In order to combat it there seem to be two lines of treatment to be considered:

(*a*) Widespan antibiotic therapy to reduce the risk of bacteræmia while the defence mechanisms are feeble. An adequate choice of agents is available to make this aspect of treatment fairly straightforward.

(*b*) Stimulation of bone-marrow activity. This is most important, since all other approaches are merely palliative. Attention must be given to the fundamental defect.

In 1933, Watkins and Giffin reported promising results from oral administration of cattle bone marrow in human granulocytopenia. Marberg and Wiles (1937, 1938) showed that the same effect on the blood could be obtained by using solely the unsaponifiable fraction of the fat—which constitutes only about 2 per cent of the bone-marrow. Holmes, Corbet, Geiger, Kornblum and Alexander (1941) found that D-batyl alcohol (D-α-octadecyl-glycerol-ether) is a component of this fraction; later, this alkoxy-glycerol was found in spleen, liver, aorta, and the red cells (Prelog, Ruzicka, and Stein 1943). Sandler (1949) reported that an unsaponifiable bone-marrow fat fraction, exerted some degree of protection to rats against benzene poisoning, and claimed that the active material was batyl alcohol, since pure, synthetic DL-batyl alcohol was also active. In 1954, Edlund claimed that synthetic DL-batyl alcohol increased the survival time of mice given total body X-radiation. Further, Brohult and Holmberg (1954) obtained a striking response in patients suffering from irradiation leucopenia, on giving orally concentrates of the liver oil of *Somniosus microcephalus* (Greenland shark) which is mainly a mixture of alkoxy-glycerol-esters (see also Brohult 1957, 1958).

Bracken poisoning in cattle produces a bone-marrow lesion which closely resembles that produced by X-radiation, and by radiomimetics, and a large part of this paper deals with the use of batyl alcohol as a stimulant of bone-marrow activity.

## Experimental

A. *Treatment of Experimental Bracken Poisoning*

(1) Use of Thiamine, Vitamin $B_{12}$, Folic acid and Leucovorin.

Two yearling heifers were fed a diet containing equal amounts of sun-dried bracken and hay, supplemented with high protein cake (3 lb. per day). One animal received *daily* injections of Thiamine 100 mg., vitamin $B_{12}$ 200 ug., Folic acid 100 mg., Leucovorin 50 mg. The second animal received none of these vitamins. The hæmatological results are shown in Fig. 1. The course of the disease was the same in both animals, and they died of bracken poisoning within a week of each other.

(2) Treatment of experimentally produced bracken poisoning with DL-batyl alcohol—antibiotic therapy.

Bracken poisoning was produced in two Welsh Black bullocks. When the

* Vitamin $B_{12}$ was supplied as " Veterinary Cytamen 100 " by Glaxo Laboratories, Greenford, Middlesex.

† Leucovorin (Ca salt) was supplied by Lederle Laboratories, Inc., New York.

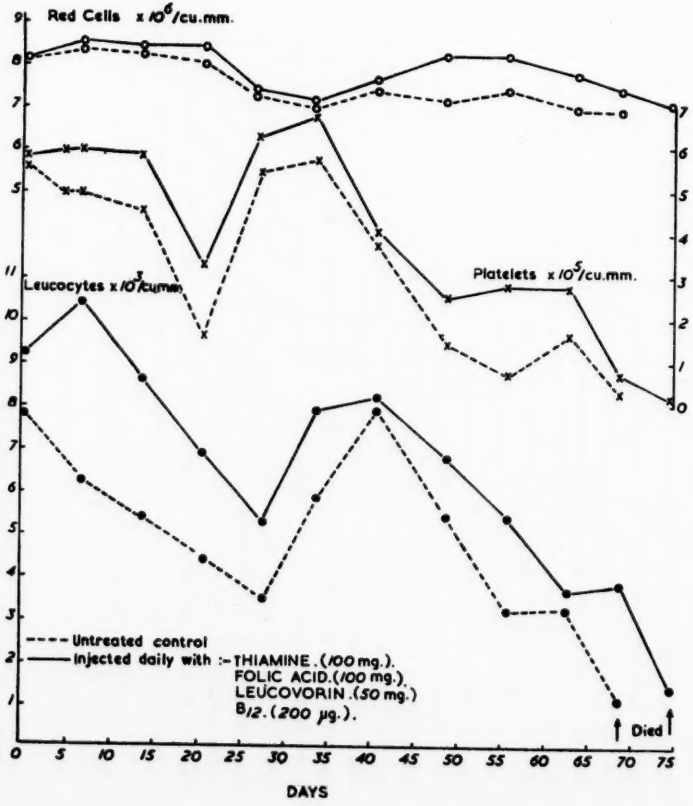

Red Cells x 10⁶/cu.mm.
Leucocytes x 10³/cu.mm.
Platelets x 10⁵/cu.mm.
Untreated control
Injected daily with :- THIAMINE. (100 mg.).
FOLIC ACID. (100 mg.).
LEUCOVORIN. (50 mg.)
B12. (200 µg.).
Died
DAYS

FIG. 1

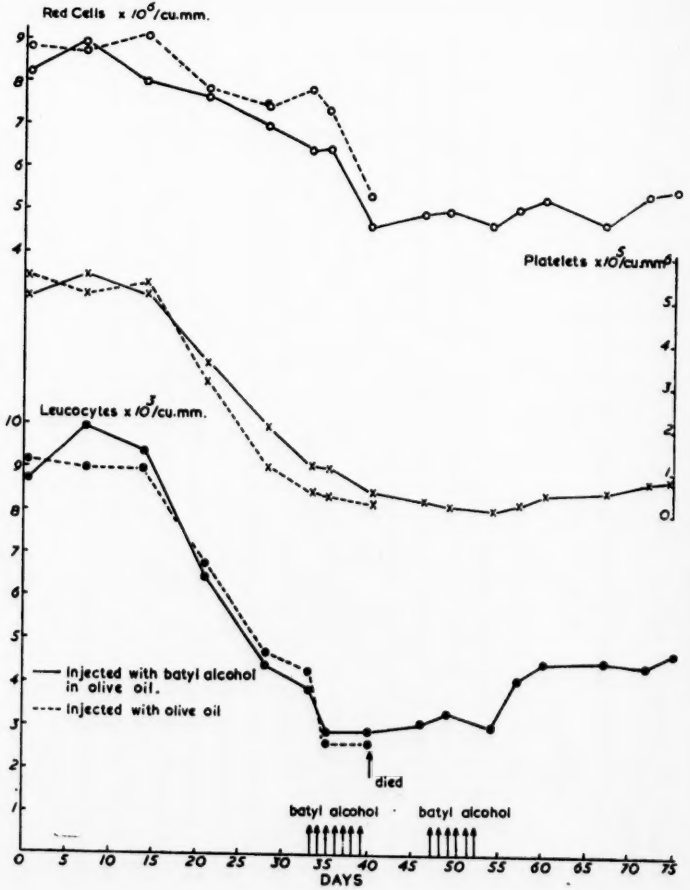

Red Cells x 10⁶/cu.mm.
Platelets x 10⁵/cu.mm.
Leucocytes x 10³/cu.mm.
Injected with batyl alcohol in olive oil.
Injected with olive oil
died
batyl alcohol
batyl alcohol
DAYS

FIG. 2

clinical symptoms of pyrexia and petechial hæmorrhages appeared, treatment commenced.

Their hæmatological status at this stage was as follows:—

| Animal | R.B.C. $\times 10^6$ | W.B.C. $\times 10^3$ | Platelets $\times 10^5$/c.mm. |
|---|---|---|---|
| C | 6.5 | 3.9 | 1.1 |
| D | 7.8 | 4.3 | 0.53 |

One animal (C), was injected subcutaneously with DL-batyl alcohol (1 g. in 10 ml. warm olive oil) for seven consecutive days. The other animal (D) received olive oil alone, by the same route. Both animals were given antibiotic therapy (daily, 500 mg. Terramycin intravenously, 3,000,000 units of Procaine-Penicillin intramuscularly)*. One day after this course of injections ended, the bullock (D) which had received no batyl alcohol, died. The treated animal (C) showed an almost imperceptible rise in leucocytes, but at least the fall was halted and the pyrexia abated. A little later it was given a further five daily injections of batyl alcohol. This evoked a considerable response in both leucocytes and platelet elements, and the animal recovered. These are shown in Fig. 2.

In a second trial the route of administration of batyl alcohol was changed. It was brought into solution with a non-ionic detergent, Tween 80, and given by slow intravenous injection (25–50 ml. of 2 per cent batyl alcohol in 5 per cent Tween 80, 1 per cent saline) to two 12-month-old Welsh Black bullocks showing clinical bracken poisoning, with a blood picture as follows:—

| Animal | R.B.C. $\times 10^6$ | W.B.C. $\times 10^3$ | Platelets $\times 10^5$/c.mm. |
|---|---|---|---|
| 2 | 7.2 | 2.5 | 0.67 |
| 3 | 7.0 | 2.0 | 0.62 |

After five days batyl alcohol and antibiotic therapy, the leucocytes and platelets rose in both animals and the pyrexia abated. The bullocks regained condition, although even after 10 weeks the white cells and platelets were below normal levels. At this point, one of the animals was given a further four daily injections of batyl alcohol, and this produced a striking response with a large increase in both leucocytes and thrombocytes. The results are shown in Fig. 3 (see overleaf).

In a further experiment with a yearling Welsh Black bullock, when poisoning became acute with pyrexia and hæmorrhage, bracken was removed from the diet but treatment with batyl alcohol was delayed deliberately. The white cells were 3,200/c.mm., the platelets 63,000/c.mm., and the temperature was 106.4° F.; we believe that we could have treated the animal successfully at this stage, but wished to know whether there was any chance of spontaneous recovery, or if the treatment could be long delayed. Six days later the white cells were 3,100/c.mm. but the thrombocytes had fallen to 26,000/c.mm. After a further six days the temperature soared to 109° F. and there was very heavy mucus discharge from the nose. The leucocytes were 1,500/c.mm. and the platelets only 2,500/c.mm.; however, the erythrocytes were normal, showing that there had not been extensive hæmorrhage. On this day the animal was injected with batyl alcohol (2 g. in 200 ml. 2 per cent Tween 80/1 per cent saline). The injection was given by intravenous drip using a

* Terramycin was supplied by Pfizer Laboratories, Folkestone; Streptomycin (Dimycin) by Glaxo Laboratories; Procaine-Penicillin by I.C.I. (Pharmaceuticals) Ltd., Manchester, and as Mylipen by Glaxo Laboratories.

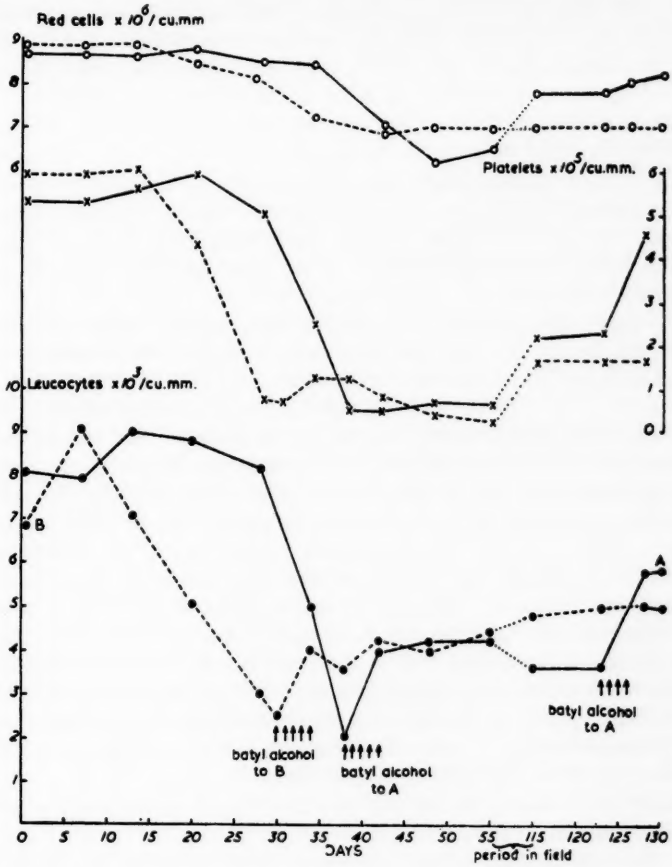



FIG. 3

flutter valve apparatus. The usual antibiotic therapy was used also. The following day, treatment was repeated and in the afternoon the temperature fell to 103.8° F. but the bullock was still very ill. Batyl alcohol injection was continued on the third day and the temperature fell to 102° F. but by this time internal bleeding had started and the circulating red cells were beginning to diminish. The next day the leucocytes had risen slightly to 1,700/c.mm. but the erythrocytes were now only 2.9 million/c.mm., the bullock was passing clots of blood in the fæces, and died that day.

In two other bracken poisoned animals (G7 and G9) where treatment had been delayed until the blood cell counts were:—

| Animal | R.B.C. $\times 10^6$ | W.B.C. $\times 10^3$ | Platelets $\times 10^5$/c.mm. |
|---|---|---|---|
| G7 | 7.4 | 1.7 | 0.15 |
| G9 | 7.1 | 3.2 | 0.08 |

batyl alcohol-antibiotic therapy was coupled with the trial of hydrocortisone (200 mg.

intravenous EF-Cortelan*) and prednisolone * (100 mg. Predsolan, intramuscularly) respectively. These cortisone derivatives seemed temporarily to improve the well-being of the animals, but in spite of this they both succumbed with severe hæmorrhages.

B. *Treatment of Field Cases*

In all we have treated 27 field cases which had been diagnosed by practitioners as bracken poisoning, and were confirmed by us. Twenty animals recovered and seven died. As we were working under field conditions, our blood figures are incomplete, but it may be interesting to quote those available; unfortunately, no platelet counts were done.

Batyl alcohol has been rendered soluble with the aid of non-ionic detergents, Tween 80 and Tween 20. The best preparation which we have found so far, and which has been applied to the more recent field cases, is made up as follows:—

Tween 80†, 8 parts (w/v), and Tween 20†, 2 parts (w/v), are added to 100 parts of water and dissolved by heating on a boiling water bath. To the hot solution is added 5 parts (w/v) DL-batyl alcohol ‡. The solution is heated on the water bath, shaking vigorously from time to time, to disperse the batyl alcohol. When a homogenous milky suspension has been obtained, the solution is cooled by immersion in cold water. When cool, the solution should be only moderately opalescent. If it is still milky, it should be returned to the boiling water bath and warmed again with shaking until it clarifies. It is then cooled again rapidly, and filtered. This solution of 5 per cent batyl alcohol is suitable for intramuscular injection. For intravenous injection, it should be diluted with 9 parts of sodium chloride solution (sterile, 1 per cent) and should be only faintly opalescent. Both batyl alcohol solutions become cloudy on standing, and on the day of use should be clarified by heating on a boiling water bath and allowing to cool. This precaution is particularly necessary in the case of the preparation for intravenous injection.

1. An Ayrshire heifer, in calf (4–5 months) showed typical bracken poisoning with profuse bleeding from the nostrils and a temperature of 106.7° F. The cow aborted. The white cell count was 2,700/c.mm. After treatment the leucocytes rose to 4,500/c.mm. a week later, and the animal recovered.

2. A Friesian heifer, 18 months old, with a temperature of 107.8° F. was bleeding profusely and not eating. It had a leucocyte count of 2,100/c.mm. After three days treatment with batyl alcohol, sulphadimidine and penicillin, the white cells had risen to 3,400/c.mm. and the animal recovered.

3. A Friesian heifer, about 18 months old, with 3,300/c.mm. leucocytes, no appetite and mucous discharge from the nostrils, but no blood, had a temperature of 106° F. After three days' treatment the temperature was normal and the white cells 4,200/c.mm. The animal recovered.

4. An 18-month-old Friesian heifer with a temperature of 104° F., mucous discharge from the nose and a poor appetite, had a white cell count of 3,600/c.mm. After three days' treatment the number of circulating leucocytes had not risen

* Kindly supplied by Glaxo Laboratories, Greenford, Middlesex.
† Obtained from L. Light & Co. Ltd., Poyle Trading Estate, Colnbrook, Bucks.
‡ Obtained from Roche Products Ltd., Welwyn Garden City, Herts.

(3,500/c.mm.), and the temperature was 104.5° F. Vaginal petechiæ were present. After a further two days' application of batyl alcohol with antibiotics, the temperature fell to normal, and the animal recovered.

5. An 18-month-old Friesian heifer was bleeding from the nose and showing a temperature of 106° F. The animal was dull and not eating. The leucocyte count was 2,600/c.mm. After three days' treatment with batyl alcohol and antibiotics, the white cell count had risen to 4,200/c.mm. and the temperature was now 104.6° F. The nasal hæmorrhage was much reduced and the animal was eating a little. Another injection of batyl alcohol was given. The animal started to eat well, and in a further two days the temperature fell to normal. The next day the temperature again rose (104.6° F.) and the nasal hæmorrhage recommenced. A day later the temperature was 105.6° F. and the heifer was injected with batyl alcohol intramuscularly. At this stage there were signs of abdominal discomfort. The animal then began to improve and was given astringent powders containing chalk, kaolin and catechu by mouth. Improvement continued and the heifer recovered.

6. A Friesian heifer, about 18 months old, showed marked petechiation of the vaginal mucous membrane and a temperature of 104° F. The white cell count was 4,500/c.mm. After three days' treatment with batyl alcohol and antibiotics, the leucocyte count had risen to 5,700/c.mm. The next day the temperature was normal, the appetite good and recovery well under way.

7. An Ayrshire heifer, about 2 years old, had a temperature of 108° F., and was very ill, with petechial hæmorrhages, and passing clots of blood in the fæces. The leucocyte count was 2,800/c.mm. After three days' application of batyl alcohol and antibiotic therapy the temperature fell to 103° F. and the heifer appeared to be much improved. Two days later the animal was eating and was turned out to the field. Unfortunately this heifer injured its leg through being crushed against a wall by another cow. The hæmatoma which followed became infected through the abrasion with anærobic organisms, resulting in gangrene with crepitation, i.e., " Blackquarter ". The leg lesion became progressively worse, and a week later the animal died. We are of the firm opinion that it was toxæmia from the leg lesion which was responsible for death, but post-mortem examination was not possible because of anthrax restrictions at the Knackery at the time.

8. A six-month-old Shorthorn calf was bleeding from the nose and had a temperature of 108° F., with a leucocyte count of only 1,900/c.mm. There were no throat symptoms as frequently appear in young animals. The calf was given two daily intravenous injections of batyl alcohol and penicillin, and was greatly improved with a good appetite. A week later it was given a further injection of batyl alcohol, and recovered.

9. An Ayrshire heifer was showing acute symptoms and had been running a temperature of 107° F. for three days. After three days' treatment the high temperature abated, and the animal recovered.

These are a selection of the successfully treated cases. The daily treatment in all cases consisted of 0.5–1.0 g. of batyl alcohol usually given by *slow* intravenous injection, together with terramycin or sulphadimidine intravenously, and procaine-penicillin intramuscularly. The terramycin or sulphadimidine was added to the batyl alcohol solution immediately before use and given as one injection. All the

farms that provided these cases had other animals with bracken poisoning, which died without being treated. Subcutaneous injection of up to 50 ml. of commercial Lamb Dysentery anti-serum was given in a few cases also. This is a rational additional line of treatment, to counteract secondary clostridial infection, which is quite common in cattle bracken poisoning (Fincham 1956).

10. A Friesian heifer was bleeding from the nose and anus, but the temperature was normal. The white cell count was 1,700/c.mm. and the red cells were only 3,000,000/c.mm.; it seemed likely that this was a very severe case, the high temperature peak having been passed. Treatment of the animal was attempted. After one day the general condition seemed to be little changed, but the white cells had risen slightly to 2,000/c.mm.; however there were now only 2,400,000/c.mm. circulating erythrocytes. A second injection of batyl alcohol and antibiotics was given, together with the transfusion of a gallon of blood. The next day the heifer was recumbent, with abdominal pain, and was passing clots of blood in the fæces. It was given a further gallon of blood from its dam (a dairy cow) and more batyl alcohol. On the day following, the animal was still alive, but with sub-normal temperature (99° F.), the leucocytes were 1,500/c.mm. and red cells 3,300,000/c.mm.; batyl alcohol and a gallon of blood were again given. The next day the white cells were 1,600/c.mm. and erythrocytes had risen in number to 4,100,000/c.mm. due to the large scale blood transfusions. On this day the heifer died, and post-mortem examination showed massive and widespread hæmorrhage, with multiple perforated ulcers of the small intestine and consequent fibrinous adhesions in the process of becoming organised. There was also a large amount of serous fluid in the abdominal cavity. Attempted treatment of a case like this seems to be hopeless from the beginning.

11. An Ayrshire heifer had acute bracken poisoning with epistaxis, a temperature of 107° F., and petechial hæmorrhages in the vaginal mucosa. The animal was treated. The following morning the heifer was passing large quantities of blood in the fæces which were tarry, and it died that day. The animal had obviously suffered a major intestinal or rectal hæmorrhage before the batyl alcohol had any time to become effective.

12. A Friesian heifer with mucus discharge from the nostrils and vaginal petechiæ had a temperature of 106° F. The animal was treated for four days, showed marked improvement, and was turned out into the field. About 10 days later, the animal showed considerable bleeding at the site of intramuscular injections, and a huge hæmatoma developed. The heifer died. A large needle (about 2 mm. bore) had been used for the intramuscular antibiotic injections so that tissue damage was greater than it need have been. Close questioning of the farmer revealed that after treatment, the heifer was kept in a field contaminated with large quantities of bracken, and it is possible that the animal may have consumed more of the plant, bringing on a second attack of poisoning.

13. An Ayrshire heifer with typical acute symptoms had a leucocyte count of 2,400/c.mm. The day after treatment commenced the white cells had increased slightly to 2,500/c.mm. However, the animal did not improve as well as anticipated; in particular the bleeding could not be controlled, so that in 10 days' time, although the leucocyte count was 2,700/c.mm. the red cells were only 1,300,000/c.mm. and the heifer died. It seems that batyl alcohol exerted a considerable effect on leucocyte

production, as their level was more than maintained, despite the serious loss of blood as signified by the extremely low erythrocyte count.

14. A four-month-old calf (Welsh Black) was brought into the department from a hill farm, suffering from acute bracken poisoning. The temperature was 105.6° F. There was a nasal mucus discharge, and marked submaxillary œdema, which is characteristic of the disease in young calves, and consequent "snoring" breathing. The leucocytes were 3,000/c.mm. when the animal was first treated. The next day the white cell count had risen to 3,700/c.mm. but the platelets were virtually non-existent (6,000/c.mm.). Treatment continued, but although the respiratory roaring became less, and the temperature fell, the calf would not eat, and was very dull. After 5 days' treatment the leucocyte count was 2,900/c.mm. and the platelets 5,000/c.mm. The bleeding time throughout had been very prolonged, and it was impossible to prevent bleeding from the sites of injection. The animal died, and post-mortem examination showed very extensive hæmorrhages. This seemed to be another case where the initial response in leucocyte production was good, but the bleeding time was so prolonged that it was impossible to control hæmorrhage.

*Bracken Poisoning of Pregnant Cows*

The toxic agent causing cattle bracken poisoning seems to function by arresting mitosis in the bone marrow, and probably in epithelial and connective tissue. In the pregnant cow there is yet another site of rapid cell proliferation, viz., the developing embryo. It might therefore be expected that this also would be affected by the bracken poison if it passes through the placental barrier. Field observations suggest that this is so.

A cow which died of bracken poisoning was near to calving, at full term. On post-mortem examination, both the carcase of the cow and the fully developed fœtus showed hæmorrhagic lesions typical of the disease. Another cow, showing early symptoms of bracken poisoning, calved an apparently full-term live calf; both the calf and its dam died three days later, with typical lesions of bracken poisoning (Jarvis-Evans 1956).

In another case, an Ayrshire heifer, in calf five months, had been treated successfully for bracken poisoning. About two weeks later, the animal was ill again with a temperature of 105° F., which responded to antibiotic therapy. However, the animal still looked uneasy, and pregnancy examination showed that a fœtus was present, but there was only a small amount of uterine fluid. The next day, the animal aborted with difficulty, and immediately began to improve; the fœtus had been dead for some time.

Several other reports have reached us from veterinary surgeons working in areas where cattle bracken poisoning is prevalent, of abortion in pregnant cows suffering from the disease, and of calves born of affected animals dying with typical post-mortem lesions of bracken poisoning, up to a week after birth.

This must be borne in mind when treating bracken poisoned cows which are in calf; uterine bleeding may then be a further complication, if abortion takes place at the time when the platelets are also at their lowest. The advisability of immediate prophylactic treatment of such calves born alive, should also be considered.

## Discussion

Prior to this present series of experiments, little success has attended the treatment of cattle bracken poisoning. Exhaustive attempts to reverse the condition, by administration of large doses of the B group of vitamins and others, have failed. Antibiotic therapy alone, has also been unsuccessful, as have been small-scale blood transfusions. Large-scale blood transfusions (a gallon a day), in cases too severe for batyl alcohol alone to be sufficient, have not been effective either.

*Significance of the results with batyl alcohol-antibiotic therapy*

Experimentally produced, together with selected field cases, have given us a total of 31 animals suffering from bracken poisoning, sufficiently acute for a positive diagnosis to be made, on the basis of external symptoms. These have all been treated with batyl alcohol together with antibiotic therapy. Twenty-three animals recovered, and eight died. The unsuccessful cases include one where the heifer died before the batyl alcohol had any time to become effective, and three had a very low red cell count, indicating that extensive internal hæmorrhage had already taken place. In these cases, the problem was the almost insuperable one of dealing with the acute complications resulting from failure of the hæmopoietic tissues. These four examples represent therefore, not so much a failure of this treatment, but an inability to apply it in time, before the complications got out of control. There were in fact only four cases where therapy might have been reasonably expected to be effective. In each of these cases there was at least a transitory increase in the number of circulating leucocytes, but the hæmorrhagic tendency could not be controlled. Some workers have commented favourably on the use of snake venom reptilase (Shaw 1956) for this purpose; other hæmostatic agents, such as " antemovis " (5-hydroxytryptamine), or " adrenoxyl " (adrenochrome monosemicarbazone dihydrate) have been suggested. We have insufficient data to comment on their efficacy at present. In assessing the value of batyl alcohol-antibiotic therapy, the important statistical figure is the percentage of animals which might have recovered spontaneously, after showing clinical symptoms. Our experience, over the past ten years, with experimentally induced bracken poisoning in thirty animals, is that none occurred. The Rowett workers (Phillipson, Naftalin *et al.* 1954, 1956) report substantially the same thing: fifteen heifers were fed bracken in different ways, and developed typical symptoms—only one recovered. Wells (1949) describes a field outbreak with twenty deaths out of a total of twenty-seven affected animals. In our earlier field observations (Evans *et al.* 1954), there were no recoveries in twenty-eight oxen showing the characteristic symptoms, although another four animals from a herd with low leucocyte counts, eventually returned to normal, but at no stage were they so severely affected as to show outward signs of poisoning. The records of one of us (Edwards), at the Veterinary Investigation Centre, Bangor, and elsewhere, also indicate almost a 100 per cent mortality rate in cattle bracken poisoning—*e.g.*, an outbreak involving twenty-two animals was encountered in 1938; they all died. The experience of veterinary surgeons acquainted with the disease is that the mortality rate is certainly as high as 80 per cent, and probably higher.

Although our numbers are limited, it seems justifiable to claim that out of the thirty-one treated animals, of the twenty-three that recovered, the prognosis in at

least sixteen (taking 70 per cent as a nominal mortality rate, which we believe to be conservative) of them would have been " grave ", and they would have died, without treatment. Of the eight which died, four were in fact in the category of being beyond treatment at the outset, i.e., prognosis " very grave " whilst the other four were in the same category as the sixteen referred to above, i.e., prognosis " grave ". This means that of the twenty animals in the category prognosis " grave " which would have died, four did die, and sixteen recovered after being given batyl alcohol-antibiotic therapy, which is a 80 per cent recovery rate.

*Factors influencing response to batyl alcohol*

Evans *et al.* (1951, 1954) describe the results of bone-marrow biopsy in a bovine animal during the development of bracken poisoning; the marrow becomes aplastic as regards the granulocytic and thrombocytic series, whilst there are still ample red cell precursors present, although there is evidence of terminal interference with the erythrocytic series as well. Naftalin and Cushnie (1954) from an examination of bone-marrow sections of bracken poisoned cattle, note that small areas of this tissue cellularly more dense, persist throughout the course of the disease. They suggest that the presence of these areas of well preserved marrow tissue may account for the transient improvement in the peripheral blood picture, frequently observed shortly before the onset of the acute stage. Batyl alcohol may exert its effect on these persistent islets of intact marrow. If none is left, no therapy at present available is likely to be successful. This conception is without factual support at present, but it might explain the variation in recovery rate, between animals which appear to be similarly affected. Some severe cases with very low white cell counts, *e.g.*, cases (2) and (8), have recovered with dramatic rapidity, while other apparently less acute conditions, *e.g.*, (5), have been slow to respond. It is probable that the extent of surviving marrow toxin depends on the rate and activity of the bracken consumed. Our experimental animals have been poisoned by feeding a fixed amount of dried bracken daily, over a period, while we have come across at least one field case where the heifer was only in contact with fresh bracken for one week; during this time the animal must have consumed an enormous quantity of the fresh fern for, some weeks later, it developed very severe poisoning and died before treatment could take effect. The chance of recovery diminishes sharply if the circulating leucocytes fall below 2,000/c.mm., with a thrombocyte count much less than 100,000/c.mm.; treatment should not be delayed beyond this critical stage, even though the external symptoms may not appear acute.

In field outbreaks of bracken poisoning it is usual for some animals to show clinical symptoms before others; even some deaths may occur. All animals at risk should be bled, their hæmatological status ascertained (especially platelet levels), and affected animals treated forthwith. Delay is fatal.

*Reaction to Batyl Alcohol Injection*

(*a*) Intravenous injection.

It is known that dispersing agents of the Tween type are toxic to animals, when injected intravenously in sufficient concentration (see Krantz, Culver, Carr, and Jones 1951; Sobel, Rosenberg, and Engel 1952). Bieri and Pollard (1954) used a 20 per cent (v/v) solution in water, of Tween 40 for dispersing carotene and vitamin A

for injection into experimental animals. Kon, McGillivray and Thompson (1955) following the procedure of the previous workers, found that 80 mg. of Tween itself per lb. body weight was tolerated by rats and rabbits. This dose level they found promptly fatal to calves; it had to be reduced to 20 mg. Tween per lb. body-weight for this species, before it could be tolerated without undue reaction. The calves that died after intravenous Tween injection showed signs of asphyxia, frothing freely through the nose and mouth, and at autopsy the lungs had nearly twice the normal weight owing to œdema.

During our early trials we occasionally experienced shock reactions in certain animals. With the considerable improvement in the solution for injection, and by administering it in a more dilute form by drip method using a flutter valve apparatus, shock has become much less common, although occasional animals seem to be sensitive. Adrenaline (5–10 ml. 1 : 1,000 subcutaneously) helps to counteract this, and we have never had serious consequences arising from idiosyncrasy. It has been reported (Gabrilove, Volterra, Jacobs and Soffer 1949) that adrenaline produces a transient leucocytosis and thrombocytosis. The effect is very rapid, with a maximal increase in neutrophils, lymphocytes and eosinophils after seventeen minutes; it is of dubious value in the treatment of bracken poisoning, where a prolonged stimulation of production over a period is required. Brief references to its value in treatment have however been made (Fincham 1956).

(*b*) Intramuscular injection.

We have found that the method of choice is intravenous injection, but in some circumstances, particularly if an animal is unduly sensitive to batyl alcohol by intravenous injection, intramuscular injection of a more concentrated solution may be employed successfully. We have given 1 g. batyl alcohol in 20 ml. Tween solution, daily for four or five days into the gluteal muscle or the biceps femoris. No local or general reactions have been observed. Owing to the poor clotting qualities of the blood in bracken poisoning cases, there may be continuous bleeding from the site of puncture; this can be minimised by using a fine needle. It is, of course, important to bear this in mind when injections of other materials are given, as supporting treatment.

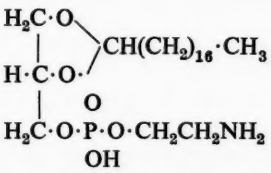
*Mode of Action of Batyl Alcohol*

Our results show that synthetic DL-batyl alcohol is capable of stimulating bone-marrow activity, after this tissue has been rendered hypoplastic through the toxic action of bracken. Other workers (Brohult 1957) have obtained promising results with alkoxyglycerolesters in irradiation treatment. The mode of action of batyl alcohol in bringing about these effects is not known at present. The naturally occurring form of this compound is the D-isomer; we do not know whether both sterio-isomers are equally effective.

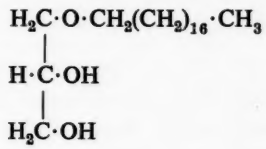
Berger (1948) examined the pharmacological properties in mice of a large variety of α-substituted ethers of glycerol, amongst which was batyl alcohol. Suspensions in gum acacia 5 per cent w/v were administered subcutaneously, or dissolved in 10 per cent. v/v aqueous propylene glycol, intraperitoneally. Batyl alcohol had no toxic effects in the doses used. Generally, α-substituted ethers of glycerol had a depressant effect on the blood pressure, reduced the heart rate, and were vasodilators; they also had an antipyretic action.

A differential analysis of the white cells, during recovery of our four experimentally produced bracken poisoning cases, with batyl alcohol antibiotic therapy, show that the response is a general one in all varieties of leucocytes, and platelet elements, indicating probably a true stimulation of bone marrow.

The wide distribution of batyl alcohol in normal animal tissues may indicate an important role, yet to be revealed, for these alkoxyglycerols in cell metabolism. Feulgen, Imhauser and Behrens (1929), by the use of certain staining techniques, discovered that the cytoplasm of many cells contain substances called plasmalogens. Later, Feulgen and Bersin (1939) reported they were complex acetal phosphatides, and a part of their molecular structure bears a distinct relationship to batyl alcohol, *e.g.*,



A typical " Plasmalogen ".



Batyl Alcohol.

It might be surmised that they are essential for the maintenance of the integrity of these cells.

Several agents are now known which depress bone-marrow activity, leading eventually to aplasia of the hæmopoietic tissues, and almost identical end lesions in the animal. These are:—

1. Irradiation damage (Loutit 1953, Barnes and Loutit 1956).

2. Several antimetabolites and antivitamins (Dustin 1954), *e.g.*, antifolic acid drugs like aminopterin, purine antimetabolites such as diaminopurine, mercaptopurine.

3. Biological alkylating agents (Bergel 1955), *e.g.*, nitrogen mustards, triethylenemelamine, dimethane-sulphonoxy-butane (" Myleran ").

4. Chemicals such as benzene, urethane, several arsenical derivatives, and certain chemotherapeutic agents.

5. The unidentified factor in Tri-Chloroethylene-Extracted-Soybean-Oil-Meal (see Mckinney *et al.* 1957).

6. The agent occurring naturally in bracken.

Some of these chemicals are used as anti-leukæmic mitotic drugs. Recent work (Ford, Hamerton, Barnes and Loutit 1957, see also Dameshek 1957) has suggested some exciting new possibilities in the treatment of animals exposed to radiation. Injection of cell suspensions from normal bone marrow or spleen into such animals led to the donated cells multiplying in each of these sites and, in effect, formed a graft of donated tissue. These take over the normal function of the animals' own cells killed by the ionising radiations, thus enabling it to survive.

The control of hæmorrhage seems to be one of the dominant problems in acute bracken poisoning of cattle; transfusion of enriched platelet preparations, the trial of other agents which decrease clotting time, and possibly bone-marrow transplants may be promising new lines for future investigation.

**Summary**

1. Attempts to prevent the development of cattle bracken poisoning by daily injections of thiamine, vitamin $B_{12}$, folic acid and leucovorin, were unsuccessful.

2. Cases of experimentally induced cattle bracken poisoning were treated successfully by a DL-Batyl Alcohol-Antibiotic therapy, provided the circulating blood cells were not below 2,000 leucocytes, and 50–100,000 platelets per c.mm. Below these values, death due to hæmorrhage and secondary infection invariably supervened.

3. Trial of this therapy in field cases gave about 80 per cent recovery rate. Data at the beginning of treatment were limited to leucocyte and erythrocyte counts, supported by clinical observations. We believe, however, that the platelet figure is the most useful indicator of prognosis.

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Table 1

Log. Maximum counts of main types of bacteria, per gm. of rumen contents.

| Weeks of bracken feeding | Coliforms | | Streptococci | | Lactobacilli | |
|---|---|---|---|---|---|---|
| | Animal fed bracken | Animal fed steamed bracken | Animal fed bracken | Animal fed steamed bracken | Animal fed bracken | Animal fed steamed bracken |
| -4 | 6 | 5 | 7 | 7 | 6 | 7 |
| -3 | 5 | 6 | 8 | 7 | - | 8 |
| -2 | 4 | 5 | 8 | 8 | 8 | 9 |
| -1 | 5 | 6 | 7 | 8 | 5 | - |
| Start 0 | 5 | 6 | 8 | 9 | - | 6 |
| 1 | 5 | 5 | 8 | 8 | - | - |
| 2 | - | 6 | 7 | 7 | 7 | 4 |
| 3 | 5 | 5 | 7 | 8 | 5 | 7 |
| 4 | 2 | 4 | 6 | - | 8 | 7 |
| 5 | 6 | 3 | 9 | 8 | 6 | 5 |
| 6 | 5 | 7 | 7 | 8 | 4 | 3 |
| 7 | 6 | 7 | 9 | 7 | 6 | 6 |
| 8 | 5 | 5 | 9 | 8 | 6 | 7 |
| 9 | 3 | 5 | 8 | 9 | 4 | 3 |

Owing to an oversight this table was unfortunately omitted from Part IV of this article which appeared in the May issue of this Journal.

# A COMPARISON OF THE REGURGITATION PHASE OF RUMINATION WITH THE ACT OF VOMITION.

By F. R. BELL, F.R.C.V.S., B.Sc., Ph.D.

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THE process known as vomiting, or emesis, occurs as a physiological mechanism in a very restricted group of animals which includes the dog, man and the cat. Usually in these species emesis is associated with nausea and it appears to be mainly, but not exclusively, a protective process developed to allow the organism to eliminate noxious substances from the stomach. The " ability " to vomit varies and perhaps vomiting has attained its highest physiological development in the dog. In certain breeds of dog, notably in those most recently domesticated such as the Basenji, the nursing bitch can vomit its stomach contents to provide semi-solid food for its puppies during the weaning period. This vomition of partly digested food exhibited by the Basenji bitch has a close counterpart in the action of certain species of birds which feed their young by regurgitation from the crop. Apparently, emesis is not always a protective mechanism, and on occasion it may be associated with nutritional processes.

Herbivorous animals do not vomit. It is possible either that the process has failed to develop, or alternatively, it has become suppressed as these animals developed the habit of ingesting large quantities of vegetable material. The anatomical specialisation of the stomach of ruminants to accommodate enormous quantities of food would appear to mitigate against emesis in these species. Owing to the inferior pabulum afforded by vegetable material for growth of proteolytic pathogenic bacteria and other organisms as compared with animal tissue, herbivorous animals do not need to develop emesis as a protective device.

Vomiting has been shown to be a sequential act combining both somatic and autonomic effector systems (Cannon, 1898). This complex pattern of activity involves salivation, spasmodic respiratory movements, movement of the gastric musculature and postural adjustments of the head and body, as well as cardio-vascular changes. Borison and Wang (1949) have shown by the experimental method that the central mechanism controlling vomiting in the dog and cat is situated in the dorsolateral border of the lateral reticular formation of the medulla oblongata, close to the dorsal vagal nucleus. Borison and Wang (1951) indicate that emetic drugs, such as apomorphine and the digitalis glycosides, do not act on the vomiting centre directly, but through a chemoreceptor region situated in the ala cinerea. They postulate further that peripheral chemoreceptors for such cations as copper affect the medullary vomiting centre reflexly via vagal afferents.

Although adult ruminants do not vomit it is interesting to note that the regurgitation phase of rumination is very similar to the act of vomition, so similar indeed, that it is reasonable to suggest that the neural co-ordinating mechanisms may be closely related. This notion is strengthened by the similarity in the cyto-architectonics of the medulla oblongata of mammals. Very young calves and goats are not herbivorous animals, for at this age the reticulum and rumen are not functional and they are effectively short circuited from the functional alimentary tract by the

œsophageal groove reflex (Watson 1941). It was considered to be possible that ruminants at this stage of development might exhibit vomiting reflexes. If this idea was proved to be correct it could suggest that the neural control of regurgitation in ruminants had developed from medullary nervous components previously associated with the regulation of vomition reflexes.

To investigate this point very young calves and goats have been subjected to the action of apomorphine and copper sulphate as central and peripheral emetics respectively. In addition adult cows have been injected with anti-emetics, and the effect on rumination examined to ascertain whether these drugs can depress rumination by suppressing regurgitation.

## Methods

The animals used were Ayrshire cows and calves and young crossbred English Goats.

Apomorphine dihydrochloride (B.P.) was prepared in sterile normal saline immediately before injection. Copper sulphate ($CuSO4.5\ H_2O$) was dissolved in distilled water, the dosage levels being calculated as the anhydrous salt. Hyoscine hydrobromide (B.P.) was prepared as a solution in sterile distilled water immediately before injection.

## Results

*Apomorphine Dihydrochloride*

(*a*) *Calves.* The dosage of apomorphine for cattle is not known so that a compromise was made at first on the known dosage of 0.01 mg. to 0.02 mg./kg. for the dog. In all cases injections were made up to 10 ml. and injected slowly into the right jugular vein.

All the calves showed signs of dejection within two minutes of the injection; they stood motionless with the head lowered and the neck extended. In almost every animal salivation was increased and the calves "smacked" their lips and licked their muzzles.

Other signs, together with the details of the individual calves are given in Table 1.

Apomorphine dihydrochloride did not produce emesis in this group of calves but signs of activation of some of the components of vomition as seen in the dog did occur.

TABLE 1

The effects of apomorphine given intravenously to calves.

| | Sex | Age in days | Wt/ kg. | Dose mg/kg. | Signs |
|---|---|---|---|---|---|
| 1 | M | 125 | 100 | 0.02 | Tachycardia within 2 minutes. Salivation swallowing after 10 minutes. |
| 2 | M | 90 | 50 | 0.02 | Dejected, tachycardia, slight lachrymation within two minutes. For 15 minutes swallowing movements, antiperistalsis in œsophagus. |
| 3 | M | 29 | 50 | 0.015 | Body heaves somewhat like retching within 7 minutes. Much swallowing, yawning. |
| 4 | F | 13 | 35 | 0.02 | Dejected, lachrymation, some swallowing. |
| 5 | F | 8 | 29 | 0.05 | Tachypnœa. Spasmodic jerking movement associated with inspiration. |
| 6 | M | 6 | 30 | 0.01 | Tachycardia, lachrymation, spasmodic movement of flanks. Swallowing. |
| 7 | M | 6 | 30 | 0.01 | Tachycardia, dejected, yawning. |

(*b*) *Young goats.* The goats were 5–7 days old and were being fed on cows' milk from a bottle. As the dose of apomorphine for the goat is not known, the amounts administered were adapted from the reactions shown by the calves. Preliminary trials showed that the results obtained from subcutaneous and intravenous injections of similar amounts of the drug were comparable. The signs manifested following the subcutaneous injection of the drug are listed in Table 2. The signs developed within a minute or two after the injection and usually they passed off within an hour.

TABLE 2

The effects of apomorphine given subcutaneously to young goats (5–7 days old).

| | Dose mg/kg. | Signs |
|---|---|---|
| 1 | 0.02 | Lachrymation, yawning, salivation |
| 2 | 0.02 | Depressed, salivation, chewing movements, tachypnœa. |
| 3 | 0.05 | Salivation, retching, licking lips. |
| 4 | 0.05 | Lip licking, salivation |
| 5 | 0.075 | Yawning, chewing movements, lip licking, increased respiratory and pulse rates, antiperistalsis in œsophagus. |
| 6 | 0.075 | Depressed, salivation, lachrymation, increased respiratory rate, oscillatory movement of material in œsophagus, quick spasmodic movements of the thorax. |
| 7 | 0.10 | Dejected looking, lip licking and swallowing, hiccoughs, signs of drowsiness deepened until 14 minutes after injection the animal had laid down and was asleep. |
| 8 | 0.10 | Lip licking, swallowing, spasmodic expiration. 5 minutes after the injection the goat lay down with drowsy appearance, 10 minutes later it was asleep. |

*Copper Sulphate*

Four calves, aged 8 days or less, were drenched with 250 ml. of warm water containing 1 g. copper sulphate. The drench was given fifteen minutes after the normal evening milk feed. The calves were kept under observation for some hours and no abnormal signs were noted.

Six young goats, less than 7 days old, were given 20 mg./kg. copper sulphate in 100 ml. of warm water. The goats were observed for several hours. No change in behaviour or demeanour was noted.

*Hyoscine Hydrobromide*

The dose of hyoscine hydrobromide for cattle is not given in the British Veterinary Codex so it was decided to use the dose of 3 to 6 mg. suggested for the horse.

Three lactating Ayrshire cows were given the drug by subcutaneous injection. In the first case the doses of hyoscine hydrobromide administered were 3 mg. (0.007 mg./kg.), 6 mg. (0.015 mg/kg.) and 8 mg. (0.016 mg./kg.) respectively. A week later the three cows were given hyoscine again but double the amount was administered.

The cows were observed carefully by attendants and no change in their rumination pattern could be detected.

## Discussion

In adult ruminants the regurgitation phase of the act of rumination is similar essentially to vomition as exhibited by the dog. In both processes a series of reflexes involving both somatic and autonomic effector systems are utilised. The central

neural controlling mechanism for vomition in the dog has been delineated in the medulla oblongata, in the midst of other loci such as the respiratory centre, the salivary nuclei, and an area which yields spasmodic respiratory acts (Wang and Borison 1950). A region which may co-ordinate rumination has been revealed in a similar topographical situation in the medulla of the sheep (Bell and Lawn 1955). In ungulates and carnivores the configuration of neuronal groupings, the disposition of the alæ cinerea and the area postrema is very much the same (Bell, 1950).

The vomiting mechanism of the dog can be activated reflexly in two ways:—

(*a*) from chemoreceptors situated peripherally in the stomach (e.g., copper sulphate); or

(*b*) from chemoreceptors situated centrally in the ala cinerea (e.g., apomorphine, cardiac glycosides).

It is known that emetics have no effect on adult ruminants but this fact would not necessarily apply to calves and goats, only a few days old, in which rumination has not developed. From the physiological point of view these very young animals with a nonfunctional rumen and reticulum could be regarded as having only a simple stomach. Even in such neo-natal ungulates emetics failed to produce vomition although signs complementary to emesis such as retching, salivation, lachrymation did occur.

These experiments yield no definite clue as to whether certain ungulates have utilised a previously formed nervous co-ordination mechanism of the medulla for the control of the regurgitation phase of rumination. It has been demonstrated that the efferent limb of the reticulo-ruminal reflex is functional very early in ontogeny (Duncan and Philipson 1952). It is probable, therefore, that the ontogenetic establishment of the adult pattern of intraneuronal connections in the medulla for the control of rumination is also established early, paralleling perhaps the early integration of vascular control mechanisms (Barcroft 1946). A further possibility is that the neural mechanisms for the control of vomition and regurgitation have diverged separately from a common ancestral co-ordination arrangement laid down very early in the medulla oblongata along with the development of the alimentary tract in mammals.

The stimulus which initiates rumination is not known. The process may be activated solely from receptors which lie peripherally, for rumination can be induced by mechanical stimulation of the œsophageal groove region (Wester 1926). The afferent and efferent channels of reflexly induced rumination are carried in the vagi in the same way as the reflex vomition induced from chemoreceptors in the stomach of the dog (Wang and Borison 1951). Peripherally placed chemoreceptors, at any rate for copper cations, appear to be absent in the young ruminant.

It may be supposed that apomorphine did in fact stimulate a chemoreceptor placed centrally in the nervous system of the calves and goats, for signs akin to those associated with vomiting were evoked, although food was not expelled from the mouth. Such chemoreceptors might be located in the ala cinerea of ruminants as they are known to be in the dog (Borison and Wang 1951). It is possible that the factors inducing the onset of rumination could be chemical in nature, affecting a chemical sensitive " trigger " zone situated somewhere in the brain stem.

Hyoscine hydrobromide which has well established antiemetic properties failed to inhibit rumination in adult cows. It is known that this drug depresses the medullary

vaso-motor and respiratory centre but in the doses used it did not exert this effect on the cows.

**Summary**

1. The effects of a central emetic, apomorphine, were studied in very young calves and goats. Emesis did not occur but other related signs such as salivation, swallowing, chewing, dejection were very prominent.

2. Copper sulphate as a peripheral emetic was also tested on very young calves and goats but produced no signs or symptoms or change in demeanour or behaviour.

3. Hyoscine hydrobromide, an anti-emetic, had no inhibitory effect on rumination in adult cows.

4. The possible relationship of vomition and regurgitation is discussed in relationship to the disposition of known arrangements of neural elements in the medulla oblongata.

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# FIGHT FOR FITNESS.

By S/Sgt. R. REAY

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ONE evening recently spectators on the Singapore Padang witnessed a wonderful display of canine acrobatics by dogs from the Army Guard Dog Unit. The dogs completed a series of tasks which could only have been carried out by superbly fit animals. Their excellent condition is the result of a combined operation on the part of the unit's Veterinary Staff and the Hygiene and Malaria Control Unit. The work of these men, few in number, affects the lives of every soldier in the Colony. The main task of the H. and M. control unit is the control of malaria. The Unit directs the work of a hundred-odd labourers who continually spray the ponds, the breeding grounds of the mosquito, throughout the island.

The word " Hygiene " in the Unit's title embraces a host of other subjects, such as a plague of cockroaches, white ants and a marauding nine-foot python.

In June 1955 the Veterinary Staff of the Army Guard Dog Unit noticed that dogs which had previously undergone long periods of patrolling without fatigue now showed signs of lassitude and listlessness after only short periods of exercise. Post mortems examinations on dogs which died suddenly during this period showed " Heartworm " to be the cause of death. Blood tests indicated that more than half the dogs were infected.

The large numbers of mosquitoes in the area gave rise to the belief that mosquitoes were in some way responsible for the spread of the disease. The Hygiene and Malaria Control Unit were called in to investigate and if possible to discover the chain of infection.

It was known that the worms, some three to four inches long, lived in the heart cavity and that the larvæ they produced required a host, or carrier, during their incubation period before entering the bloodstream of another dog and thus spreading the infection. No available drug was capable of killing the adult worm so there remained two methods of beating the disease; by killing the larvæ in the bloodstream or by destroying the carrier in which they incubated.

The first method was tackled by the veterinary staff who treated the infected dogs with various drugs known to be lethal to larvæ. Although there was a slight improvement in most of the dogs only a very small percentage showed a negative larvæ count by the end of the course. Meanwhile, the Hygiene section were engaged on field work to determine the other link in the infection chain, the carrier. This work was directed by Lt. R. D. Hughes, R.A.M.C., the entomologist officer.

Two National Servicemen, Ptes. C. M. Hughes and D. K. Mugford, R.A.M.C., spent several nights in the kennels under a mosquito net, open at one end. As a mosquito alighted on one of them, the other would scoop it deftly into a test tube which was then labelled with the time and place of the " capture ".

Meanwhile it was discovered that the larvæ came to the peripheral or skin level blood vessels only between eight and eleven at night. From the log of the mosquito trapping a statistical table was drawn up. It showed that one particular mosquito, *Mansonia Uniformia*, was many times more prevalent in the area during the period in which larvæ in the dogs were in the skin area. Further experiments proved *Mansonia* to be the culprit.

In the case of practically every other mosquito, elimination would have been a simple matter of spreading oil on the nearby Hyacinth ponds in which they bred, thus choking the young mosquitoes who breathe through the surface of the water. *Mansonia*, however, is much more cunning. The adult of this species lays its eggs underneath the leaves of water hyacinth plants. When hatched the larvæ drop from the leaves, sink beneath the surface, attach themselves to the stalk of the plant and breathe through it until they reach the adult stage. Destruction of the mosquitoes was achieved finally by the use of a soluble insecticide in pellet form provided by a commercial organisation. When dropped into the Hyacinth ponds it dissolves slowly and remains effective for six months. A commercial compound in the form of a fog spray was used in the kennels to rid the area of the adult *Mansonia*.

About thirty new dogs were brought from England during the first few months of 1956 to replace the infected animals. As " Heartworm " cannot be detected until eight months after initial infection, results were not known until December. Tests have proved that not one dog of those thirty reinforcements has " Heartworm ".

# *OBITUARY*

## Professor Norman James Scorgie, M.A., B.Sc., M.R.C.V.S.

NORMAN JAMES SCORGIE, Courtauld Professor of Veterinary Hygiene and Animal Husbandry at the Royal Veterinary College, died on Monday, February 10th, 1958. His death occurred suddenly from a heart attack. Professor Scorgie was in Iran under the auspices of the World Food and Agriculture Organisation. He was on his second visit to Iran where he had been assisting the University of Teheran in the organisation of the Animal Husbandry Department of the Veterinary School and advising the Government on matters appertaining to animal husbandry in the field.

Norman Scorgie was born in 1908 in the village of Old Meldrum, Aberdeenshire. Old Meldrum is in an agricultural district in the area known as Buchan which has achieved fame because of the number of great scientists and men of letters who have originated from there. His father was the bailiff on the farm of a large mental hospital. He attended the village school and in 1921 he entered the second year of the secondary course at Inverurie Academy. He was at the academy until 1926 when he won an arts scholarship in the Aberdeen University Bursary Competition. He entered the University as a student in the Faculty of Arts in 1926 and graduated M.A. in June 1929. His intention was to read for a degree in agriculture but during his early student days he became interested in natural science so he entered the Faculty of Science of the University and graduated B.Sc. in 1931. His career at the University was good and he was a hard and very diligent worker. He took part in student social affairs and played an active part on the S.R.C. He played tennis and Association football and was in the O.T.C.

About the time when he took the B.Sc. degree the Colonial Office was offering veterinary scholarships to graduates in science with the view that they would qualify as veterinary surgeons and then work in the Colonial Veterinary Service. Scorgie entered the London College. He was a good student and he had a creditable academic career. He qualified M.R.C.V.S. in July 1935. He was expected to fulfil his contract and join the Colonial Veterinary Service but it happened that owing to retrenchments in the Services he and several other young men were not needed and they were released from their obligation.

After acting as locum tenens in Wiltshire for a short time he was appointed to a junior post in the Research Institute at Camden Town. He assisted Dr. Minett and Dr. Stableforth in the intensive research being conducted at that time on mastitis and contagious abortion and trichomoniasis in cattle. In 1937 he was transferred to the Department of Veterinary Hygiene and Animal Husbandry. He served as Lecturer and Reader in that department under Professor W. C. Miller. He took a particular interest in artificial insemination and in poultry husbandry. When his department was evacuated to Sonning during the war he assisted in the establishment of the Reading A.I. Centre and was a member of the A.I. Committee. He collaborated with the late Dr. Black, of Reading University, on poultry husbandry problems and together they were able to report on the first successful application of A.I. in fowls. He was interested also in endocrinology, particularly as related to the problem of infertility in cattle. He was one of the first to use synthetic stilbœstrol in the field.

Professor Norman James Scorgie, M.A., B.Sc., M.R.C.V.S.

During the evacuation period facilities for teaching and research were very limited on the College premises but Scorgie took full advantage of the opportunity to make contact with and work with members of the staff of Reading University Faculty of Agriculture working in the Dairy Research Institute, at the A.I. Centre, in the laboratories, and at the University farm. He read widely and neatly and methodically compiled a most extensive reference file to which he could turn and find the answer to almost any veterinary question one could pose.

When staff and students returned to Camden Town during the long vacation in 1945 most of the task of rehabilitating the Animal Husbandry Department fell to Scorgie for his chief, Professor Miller, left at that time to become Director of the Animal Health Trust Research Station at Newmarket. The task was done smoothly and efficiently and teaching was resumed without interruption in October. His teaching duties were heavy because for some considerable time there were only two on the staff of the department, himself and the biochemist. In 1946 he was appointed Professor and later, as the College's financial state permitted, he was able to add additional members to his staff. Gradually, as the teaching duties could be shared, there was time for a modest research programme covering nutritional and endocrine problems, building construction and ventilation, and artificial insemination. He was able also to devote some time to advisory work with regard to breeding, nutritional, and housing problems on farms, studs and kennels. This aspect of his work met with much appreciation and in consequence the time for his own personal approach to research activities was limited. When the College acquired its new field station and farm at Little Heath, Professor Scorgie was able to give valuable assistance in the stocking and planning for the gradual change in the farming system to that of a mixed farm. His department began to use the farm for teaching purposes as soon as the College took possession and he was looking forward to the day when it could become a vital centre for research.

During his period as head of the Department of Animal Husbandry and Veterinary Hygiene he had many difficulties to face. Shortage of staff, financial stringency and a want of adequate facilities for research. In spite of these things he made the best of the limited opportunities and did a good job. In 1951 he was appointed Professor of Veterinary Hygiene in the University of London.

Norman Scorgie was a small, spare man. For many years he suffered from chronic ill-health and at times he was in considerable pain for he was a victim of peptic ulcer. In spite of this he led a very active life and worked very hard. He was a great reader and his tastes in literature were very wide. In consequence he was a good conversationalist and there were few topics on which he could not join competently in any discussion. His life ran to a regular time table, probably this may have had its origin in ill-health. His office was one in which there was a place for everything and everything was in its place. He spent many hours daily in reading past and current literature appertaining to his particular discipline. He was blessed with a good memory which he fortified by a comprehensive filing system of his own design so that he became a veritable encyclopædia to whom his less methodical colleagues turned for reference and information. Although he came from farming stock, his great fund of knowledge was based more on the library rather than on his own practical experience in the field. This, of course, is in

keeping with modern trends in educational circles. Many professors in a great variety of callings could not practise what they preach. About four years ago Scorgie's illness became almost unbearable and he submitted himself to the surgeons in hope of relief. The results following a partial gastrectomy were remarkably good. Within a few weeks he was relieved completely and he was fitter than he had been for years. Socially he was always good company but after the operation he seemed to gain a new lease of life and it was good to see the change when he could enjoy normal food without any thought of its revenge. It was this great change in his physical state which encouraged and allowed him to accept the invitation to visit Persia. It is easy to be wise after the event, but there is no doubt that he attempted too much and too soon after an operation which often leaves a legacy of circulatory disturbances which take a long time to settle to normal rhythm and function. The news of his death came as a great shock to his colleagues and even now it is hard to realise that this relatively young man who left for Iran in such good spirit has passed beyond the veil. The sympathy of all his colleagues and friends goes out to his widow and two daughters.

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## *REVIEWS*

DISEASES AND PARASITES OF POULTRY, by E. H. Barger, L. R. Card and B. S. Pomeroy. 5th edition, 400 pages, 84 illustrations. Published by H. Kimpton, London, 37s. 6d. 1958.

FIRST published in 1935, Barger and Card's well-known textbook has been revised for the fourth time. Dr. B. S. Pomeroy, Professor of Veterinary Bacteriology and Public Health, St. Paul, Minnesota, has joined the main authors. Although the fifth edition contains 84 illustrations few of these are new or original.

The first chapter deals mainly with the Mortality Problem but the majority of references refer to records of the 1920–40 era. Is there much value in filling one whole page with statistics of the monthly distribution of mortality in the Michigan Egg Laying Contest for the 1922–37 period? As a contrast only four references deal with the mortality picture from 1950 onwards.

The Section dealing with Anatomy (and Physiology) does not appear to be as up to date. For example, it is stated that the " air moves more or less continuously through the system (respiratory) instead of in and out." The renal-portal system is not mentioned under the circulatory system, and Bradley (1915) is still quoted as the authority on the lymphatic system. The leukocytes " are divided into five principal groups " but these are not named. The function of the Bursa of Fabricius is said to be not understood. Spermatozoa are not mentioned under the Reproductive System of the Male nor in the Index. Five full pages are devoted to Caponising Poultry by the surgical method, but Chemical Caponisation is dealt with in six and a half lines.

Quoting Hill's 1884 method, the authors say that surgical treatment for Ascites " may be worth while in the case of valuable birds ". It is interesting to note that " cropectomy " can be performed with ease on week-old chicks without an anæsthetic or the use of aseptic technique. If hæmorrhage occurs following dubbing apparently it can often be much reduced by " laying a clean feather over the cut surface ".

A more up-to-date statement is that Leghorn baby chicks can be de-combed using a fine pair of sharp scissors, without pain or bleeding to any extent.

Although 38 lines are devoted to the use of sulpha drugs for treating B.W.D., only four refer to furazolidone. The diagnosis of Infectious Laryngo-Tracheitis is said to be based on its typical symptoms and lesions and rapid spread in a flock. No mention is made of any laboratory procedure for identifying the causal virus which is termed *Tarpeia Avium*, whilst that which causes Infectious Bronchitis is known as *T. pulli; Tortor furens* is the name given to the causal virus of Newcastle Disease, and *Miyagawanella psittaci* is the causal virus for Psittacosis. These names will be new to most veterinary surgeons in this country.

Although the Avian Leucosis Complex is dealt with in detail (11 pages) it is curious that there are no references in the text to any research work after 1947, except for one brief mention by Burmester and Waters, taken from the U.S. Department of Agriculture's Year Book for 1956. That none of the various forms of this disease can be prevented by vaccines or other prophylactic measures is acknowledged. Selective breeding and the isolation of young birds, particularly during the first two weeks after hatching, are stressed in conjunction with sanitation for the control of the Avian Leucosis Disease Complex.

The effective use of antibiotics for Ornithosis and Infectious Synovitis is mentioned, such up to date measures offering a contrast to the general tone of the text.

In this country one finds that Infectious Avian Encephalomyelitis is of increasing importance, but unfortunately this book contains no references to the subject dated after 1942. Coccidiosis receives full consideration but although nicarbazin, nitrofurazone, nitrophenide and sulphaquinoxaline are mentioned, no details as to the levels to use these drugs are given, and there is no mention of sulphamexathine. On page 240 relative to the control of Blackhead the authors state " the newer drugs . . . are very useful under what may be called emergency conditions, but they should not be considered as substitutes for sanitation and hygiene in rearing turkeys ". Bearing in mind the vast quantities of drugs sold for the prevention and cure of blackhead, there must have been very many emergencies in the U.S.A. and elsewhere during the past 10 years.

The ninth chapter deals with Nutritional Disorders. Alfalfa meal and certain fish oils are mentioned as rich sources of this vitamin, but there is no mention of synthetic vitamin A. The anti-oxidant D.P.P.D. is recommended for preventing Crazy Chick Disease, yet the American authorities banned this medicament two years ago. It has been replaced by B.H.T. or B.H.A. There are references to synthetic nicotinic acid but none to pantothenic acid.

No new information is given regarding Aspergillosis, but for the treatment of Favus a 2 per cent solution of certain quarternary ammonium compounds is said to be valuable, being non-toxic. Cage Layer Fatigue is mentioned, but no indication is given that the ætiology probably concerns calcium metabolism.

De-beaking is not mentioned in the index although it is referred to on page 296 in the section dealing with Cannibalism. Painting the windows of poultry houses red to prevent cannibalism is stressed, but from the opinion of the authors and from a practical standpoint it is much more important to provide brooding conditions which will make it unlikely that cannibalism will ever get started. They mention

proper environmental temperatures, and that the birds should be given plenty of room. One wonders how this latter aspect can be related to present-day broiler production?

Round Heart Disease receives mention on page 302 but no references are given with a date after 1947, and J. E. Wilson's researches are not included. There is a notable lack of reference to British research work. In a sense the eleventh chapter is the best in the book, dealing with poisonous drugs and chemicals, moulds and fungi, plants and seeds, insects and other poisonous substances. But the short appendix at the end of the book dealing with drugs and disinfectants is disappointing. For example, whilst antibiotics are mentioned no indication is given as to the levels to which these should be included in feeds for controlling disease. The dose of carbon-tetrachloride for the fowl is given as 1 c.c. whereas much larger doses can be given with safety. Although listed earlier in the text, neither piperazine, gammexane nor barium-antimonyl tartrate are included in this list of drugs. Kamala is mentioned as a vermifuge against tapeworms, but it is not included in the section dealing with tapeworms on page 355. Clearly this appendix needs further revision.

It is regretted that this text book, which is so excellently produced, should provide such disappointing reading to the reviewer in view of the very high esteem in which the three authors are held throughout the poultry world.

### Inco-Mond Magazine No. 6

THE sixth issue of the Inco-Mond magazine is now available. The leading article in this issue deals with the use of nickel-containing stainless steel in the manufacture of fatty acids. Among the other articles are descriptions of a unique air-conditioning process at one of Inco's mines and the use of iridium-type alloys in the manufacture of Swan pens. Other uses of Mond products in portable electric tools, marine chronometers, glass figurines, and equipment used in the dairy for teaching students at Aberystwyth University are featured.

Inco-Mond Magazine is obtainable free on request from the Mond Nickel Company, Limited, Thames House, Millbank, S.W.1.

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## *NOTICES*

### New Veterinary Product

THE DISTILLERS COMPANY (BIOCHEMICALS), LIMITED announces a reduction in the prices of their streptomycin preparations, "Streptaquaine" Solution Veterinary, "Mixtamycin" Solution, Streptomycin DC(B)L and Dihydrostreptomycin DC(B)L. The new prices, which came into effect on Monday, May 12th, 1958, can be obtained from the Veterinary Department, The Distillers Company (Biochemicals) Limited, Broadway House, The Broadway, Wimbledon, London, S.W.19. (Telephone: Liberty 6600.)

The company also announce the availability of two new veterinary packs. "Distavone" 4.5 Veterinary: Each vial contains 500,000 units potassium peni-

cillin G, 1,500,000 units procaine penicillin G and 2.5 grammes dihydrostreptomycin sulphate. The synergistic action of the combination gives an increased effect against susceptible organisms. " Distivit " B12 Veterinary: " Distivit " can be supplied in a larger vial; a 30 ml. vial containing 250 micrograms of vitamin B12 per ml. Flexibility in choice of dosage at economical levels is now possible with the new large multi-dose vial. Prices are as follows: " Distavone " 4.5 single vial 10s. 9d., " Distivit " B12 30 ml. single vial 23s. 6d.

The company also introduce a new veterinary product—" Streptaquaine " Sulpha Oral Suspension Veterinary.

A ready prepared suspension for action against scour, this new preparation combines dihydrostreptomycin with sulphadimidine for a double-barrelled attack on bowl infections in veterinary practice. Apart from these two soluble antibacterials the suspension contains the traditional bowel absorbents and astringents, Kaoline and Pectin. This liquid preparation is available in a 16 fluid ounce dispensing pack.

Price as follows: " Streptaquaine " Sulpha Oral Suspension Veterinary, bottles of 16 fluid ounces, 27s. 6d. The above products are subject to the usual discount rates available to the veterinary profession.

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**Erysilin**

GLAXO LABORATORIES, LTD. announce the introduction of Erysilin, a new vaccine in emulsion form for immunisation of pigs against swine erysipelas. It is available on the home market in 20cc. and 50 cc. vials.

The vaccine contains killed Erysipelothrix Rhusiopathiæ absorbed on aluminium hydroxide. During the past 18 months Erysilin has been tested on over 10,000 animals during field trials. Results indicate an exceptionally high degree of immunity.

Glaxo also announce the introduction of Predsolan tablets (each tablet containing 1 mg. prednisolone as the acetate). The tablets are intended primarily for the small animal practice where in this convenient dosage form systemic prednisolone may be indicated in the treatment of serious burns, some skin conditions and certain allergic conditions to supplement topical therapy. The preparation can also be used in conjunction with local injections of corticosteroids for some inflammatory joint and tendon lesions. The product was available from 23rd June and is supplied in bottles containing 25 tablets.

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EVANS MEDICAL have pleasure in announcing that pure, stabilised, crystalline trypsin is now available under the trade of Trypvet Novo. The adoption of this new title and the presentation of the product as a veterinary speciality now enables this enzyme to be used as an economical routine adjunct to antibiotic therapy in the treatment of mastitis, as well as in the treatment of localised necrotic conditions.

# *NEWS*

## CELEBRATION OF THE BICENTENARY OF THE GEIGY ORGANISATION

Extract of a speech delivered by Mr. Charles F. Gysin, Chairman of Geigy (Holdings) Limited, of Manchester, at a reception on May 28, to celebrate the bicentenary of the Geigy Organisation.

"THE scientist today is rendering a greater service to his fellow men than ever before, yet the scientist has never been so misunderstood as he is today.

There is misgiving in the layman's mind about science and not all of it springs from fear of the atomic bomb, though that no doubt has a good deal to do with it.

But even developments of a peaceful nature, like the use of nuclear energy, and possibly some advances in medical science, are looked upon with some suspicion.

The man in the street, not unnaturally, fails to distinguish between the different branches of science. He emerges from his bewilderment with an impression that scientists in general have 'gone too far', that they are juggling with forces which are better left alone.

It is the task of all of us who are concerned with scientific development to dispel this mistrust of science in an age when the world should be embracing its blessings. It is important that people everywhere are encouraged to support scientists, to accept the products of scientists and, not least, to become scientists.

In the simple but expressive phrase of the schoolboy, 'science is a good thing'. That is the message we must spread."

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### £1m. Project of Smith Kline and French Laboratories Ltd.

THE building of new pharmaceutical research and development laboratories, factory and offices for Smith Kline and French Laboratories Ltd. has begun this month on a nine-acre site at Welwyn Garden City.

Smith Kline and French are the manufacturers of such well-known products as "Benzedrine", "Dexedrine" and "Drinamyl". They also produce nearly all the country's requirements for nitrofurans, a large group of drugs used extensively, particularly in veterinary medicine.

The new establishment, which will replace the present one at Camberwell, London, will cost £1 million and has been designed to allow for both horizontal and vertical expansion. The structure will be of brick-clad reinforced concrete. An interesting constructional feature will be the coffered roof of advanced design, also in reinforced concrete and combining lightness with strength.

The company's chemical factory at Tonbridge, Kent, is to continue manufacture.

This new project at Welwyn exemplifies the constant endeavour of leading pharmaceutical houses to maintain the advance in pharmaceutical research and development.

In addition to producing such nitrofuran drugs as "Furadantin", "Nefco" and "Neftin"—the latter two for use in veterinary medicine—research continues to discover new nitrofuran drugs within the groups for use in both these fields.

## P.I.D.A.'s Veterinary Advisory Committee Named

SEVEN prominent members of the veterinary profession are to form the first committee appointed by the Pig Industry Development Authority to advise them on their work for the British pig industry.

Professor A. Robertson, M.A., B.Sc., Ph.D., M.R.C.V.S., F.R.I.C., F.R.S.E., Director of the Royal (Dick) School of Veterinary Studies, University of Edinburgh, will act as Chairman of the Veterinary Advisory Committee which represents a wide range of veterinary work and interests.

The members have been chosen after consultation with the Royal College of Veterinary Surgeons, the British Veterinary Association, the Ministry of Agriculture, Fisheries and Food, and the Department of Agriculture for Scotland.

Those who have accepted P.I.D.A.'s invitation to serve on the Committee are: Professor L. P. Pugh, M.A., B.Sc., F.R.C.V.S., of the School of Veterinary Medicine, Cambridge University, who is Chairman of the Technical Committee on Pig Research of the Agricultural Council; Dr. N. Barron, B.Sc., Ph.D., M.R.C.V.S., principal of the Vitamealo Advisory Service; Mr. J. T. Done, B.V.Sc., M.R.C.V.S., of the Ministry of Agriculture, Fisheries and Food, Central Veterinary Laboratory, Weybridge; Mr. H. I. Field, M.Sc., M.R.C.V.S., of the Ministry's Veterinary Investigation Service and a member of the Advisory Committee of the Pig Progeny Testing Board; Dr. D. Luke, B.Sc., M.R.C.V.S., Senior Veterinary Research Officer of the Veterinary Research Division, Northern Ireland; and Mr. D. F. Oliver, B.Sc., M.R.C.V.S., Honorary Secretary of the British Veterinary Association and Official Veterinary Surgeon to the National Pig Breeders' Association.

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## Use of Approved Chemical Agents for the Cleansing of Dairy Equipment

APPROVAL has been given by the Minister of Agriculture, Fisheries and Food under the Milk and Dairies Regulations, 1949/1954, for the use of the undermentioned product as an oxidising or preservative agent in the cleansing of dairy equipment.

*Name of Product*: Eydosan; *Name of Firm*: Thomas Pettifer & Co., Ltd., Eydon, Rugby.

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